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(54) Title: PROCESS FOR PURIFICATION OF HMG-CoA REDUCTASE INHIBITORS

(57) Abstract

A process for the purification of an HMG-CoA reductase inhibitor employing preparative high performance liquid chromatography as well as a pharmaceutical composition comprising the HMG-CoA reductase inhibitor and pharmaceutically acceptable carrier.

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TITLE OF THE INVENTION

PROCESS FOR PURIFICATION OF HMG-CoA REDUCTASE INHIBITORS

BACKGROUND OF THE INVENTION

This is a continuation in part of U. S. Serial Number 07/668,831, filed March 13, 1991.

High product purity is an important criterion for the manufacture of a safe and effective pharmaceutical. HMG-CoA reductase inhibitors, such as lovastatin, simvastatin and pravastatin, are a recently introduced new class of cholesterol-lowering agents that effectively lower plasma cholesterol but must be taken on a long term basis. Thus it is particularly critical that HMG-CoA reductase inhibitors be administered in the highest possible purity.

Standard methods for the purification of organic molecules involve multiple recrystallization steps and employ large amounts of organic solvents. It would be highly desirable to employ a purification process that would yield a product purity of at least 99.5%, use no more than one crystallization with a recyclable solvent and be adaptable to high production volume.

High performance liquid chromatography (HPLC) is commonly used for the analytical determinations of compound purity. HPLC for large scale industrial solution preparations (preparative HPLC) has been employed in the separation and and purification of proteins but it is believed not to have been employed in the large scale purification of relatively small molecules such as HMG-CoA reductase inhibitors.

DETAILED DESCRIPTION OF THE INVENTION

This invention relates to a process for the purification of HMG-CoA reductase inhibitors by high performance liquid chromatography to yield a product of purity of at least 99.5%. The HMG-CoA reductase inhibitors within this invention include, but are not limited to, lovastatin, simvastatin, pravastatin, fluvastatin and mevastatin. The HPLC process of this invention offers a significant advantage in that no recrystallization is required to obtain a purity of at least 99.5% and typically only crystallization is employed. In addition, the HPLC process of thisinvention may be carried out with only one organic solvent, thus minimizing the need for recycling of solvent.

The process of this invention herein may employ either normal phase HPLC or reverse phase HPLC. For HMG-CoA reductase inhibitors exhibiting a tetrahydro-pyranone ring, such as lovastatin and simvastatin, the reverse phase procedure is preferred. The column packing may be uncoated silica, coated silica or porous graphitic carbon. The term coating as used herein includes both a physical and a chemical bonding of the binding group.

The crude HMG-CoA reductase inhibitor of approximately 85% or higher purity is dissolved in an organic solvent or a solution of an organic solvent and water. The mixture may be buffered to a pH between 2 and 9 with an organic or inorganic salt. Buffers may include, but are not limited to, Tris-acetate, or acetic acid/ammonia. The resulting solution is placed on an HPLC column. The column packing may be regular or irregular in shape. The diameter of the packing material may range from about 1 μm to about 100 μm. Preferably, the packing material is irregularly-shaped octadecylsilane and the diameter of the packing material is between about 3 μm and about 30 μm.

The column packings include, but are not limited to, silica, octylsilane, dimethylsilane, octadecylsilane, cyano-silane, or polystyrene-divinylbenzene copolymer with an organosilyl stationary phrase.

The column diameter may vary from 5 cm to 80 cm. The usual column length is approximately 25 cm. The column length may be extended as needed to effect the separation. Lengthening of the column may be accomplished by linking additional columns in series.

In general, the column is packed with the coated or uncoated silica in the following manner: the packing material is slurried in ethanol. The slurry is then transferred into the column and compressed at 55 bar using Dynamic Axial Compression (D.A.C.*), a procedure described in U. S. Patent 3,996,609 and French Patent 73.07278. Alternatively, the column may be radially compressed. The ethanol is displaced with mobile phase. After packing the column is tested by collecting serial fractions and evaluating those fractions by standard analytical techniques.

The eluant is an organic solvent or a solution of an organic solvent and water which may also include a buffer of pH 2 to pH 9. The eluant is generally the same solvent or solvent mixture as the dissolving solvent but, if desired, the eluant may have a different composition. Preferably the eluant contains the same organic solvent and aqueous modifiers as the dissolving solvent. If desired, a gradient elution of the mobile phase may be employed to more rapidly elute the HMG-CoA reductase inhibitor through the column. The chromatography may be carried out at an operating temperature appropriate to the solvents employed, however a range of about 15° to about 60°C is preferred. In the preferred embodiment, isothermal conditions are maintained throughout the separation. Detection of the HMG-CoA

reductase inhibitor may be by spectroscopic means or by other physical means such as optical rotation or refractive index. The preferred means are by ultraviolet absorption or refractive index. After the HMG-CoA reductase inhibitor peak of interest is collected, a portion of the solvent is removed and an aqueous solution is added to crystallize the HMG-CoA reductase inhibitor. Generally, about one-third of the solvent mixture is removed and water is employed to crystallize the HMG-CoA reductase inhibitor. Alternatively about two-thirds of the solvent mixture is removed to crystallize the HMG-CoA reductase inhibitor. The crystallized inhibitor is then filtered and dried to yield a product of purity of at least 99.5% and with an overall yield of about 90%. Product purity is determined by HPLC relative to a reference standard. Yield is determined by weight.

The crude HMG-CoA reductase inhibitor is prepared following any of the literature procedures well known to those skilled in this art. Packing materials of uncoated or coated silica are commercially available. Porous graphitic carbon as a packing material is also commercially available in pre-packed columns.

The organic solvent, employed as the dissolving solvent or the eluant, is selected from acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride, chloroform or a mixture thereof. The percent of organic solvent in an organic solvent/water mixture may vary from about 10% to about 90% organic solvent, preferably 65% to 75% organic solvent.

The present invention is also directed to purified forms of HMG-CoA reductase inhibitors or their salts which have a purity of at least 99.5%. In one class of the invention are lovastatin, simvastatin and pravastatin of purity 99.5% or better. Also included with the present invention are pharmaceutical compositions containing a HMG-CoA reductase inhibitor or a salt thereof of purity of at least 99.5% and particularly lovastatin, simvastatin and pravastatin of purity of at least 99.5%.

If desired the amount of any residual solvent, particularly acetonitrile, may be decreased by dissolution of the purified HMG-CoA reductase inhibitor in aqueous methanol and crystallizing therefrom as shown below in Example 6.

The pharmaceutically acceptable salts of the compounds of this invention include those formed from cations such as sodium, potassium, aluminum, calcium, lithium, magnesium, zinc, and from bases such as ammonia, ethylenediamine, N-methyl-glucamine, lysine, arginine, ornithine, choline, N,N'-dibenzylethylenediamine, chloroprocaine, diethanolamine, procaine, N-benzylphenethylamine, diethylamine, piperazine, tris(hydroxymethyl)aminomethane, and tetramethylammonium hydroxide.

The purified compounds of this invention may also be administered in combination with other cholesterol lowering agents such as those which inhibit an enzymatic pathway in the biosynthesis of cholesterol. Example of such agents would include

but are not limited to squalene synthetase inhibitors, HMG-CoA synthase inhibitors, and squalene expoxidase inhibitors. Illustrative of such inhibitors are the squalene synthetase inhibitors described in U. S. Patents 5,053,425; 5,055,487 and 5,026,554. Other cholesterol lowering agents that may be administered include niacin, probucol, and the fibric acids, clofibrate and gemfibrozil. Appropriate daily dosages for adults are niacin (2-8 gm), probucol (up to 1000 mg), clofibrate (up to 2 gm) and gemfibrozil (800-1500 mg).

The compounds of this invention may also be coadministered with pharmaceutically acceptable nontoxic cationic polymers capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract. Examples of such polymers include cholestyramine, colestipol and polymethyl-(3-trimethylaminopropyl)imino-trimethylene dihalide> The relative amounts of the compounds of this invention and these polymers is between 1:100 and 1:15,000.

EXAMPLE 1

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water which was injected onto a 5 cm diameter, 25 cm long stainless steel column packed with 10 μm, irregular-shaped octadecylsilane HPLC packing material (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 260 mL using UV

detection at 254 nm. The lovastatin fraction was eluted at K' = 2.0-3.0. K', the capacity factor, is related to the retention time as described in USP - XXII (p. 1565; 1990). The resulting solution was concentrated by removal of one-third of the solvent, and the lovastatin was crystallized by the addition of water to give an acetonitrile concentration of approximately 25-30%. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered in an overall yield of 90%.

EXAMPLE 2

Lovastatin at a concentration of 2.3 g/100 mL was dissolved in a mixture of 70% acetonitrile/30% 0.02 M Tris-acetate (pH 7.4). The solution was loaded onto a 5 cm diameter, 25 cm long stainless steel column packed with 10 μm, irregular-shaped octadecylsilane (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70% acetonitrile/30% water and the flow rate was approximately 150 mL/minute. Detection was by ultraviolet absorption at 254 nm. Lovastatin was eluted at K' = 2.0-3.0. The lovastatin peak was collected and one third the volume was removed by vacuum distillation at $\leq$ 40°C. Water was added to bring the acetonitrile concentration to 25-30%. The lovastatin was filtered and dried in vacuo at $\leq$ 40°C. Lovastatin with a purity of $\geq$ 99.7% was recovered in an overall yield of $\geq$ 90%.

EXAMPLE 3

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water buffered with 0.02 M Tris-acetate (pH 7.5). The solution was loaded onto a 5 cm diameter, 25 cm long column packed with 10 μm, irregular-shaped octadecylsilane HPLC packing (RG1010-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 265 mL using UV detection at 254 nm. The lovastatin peak eluted at K' = 2.0-3.0. The resulting solution was concentrated by removal of one third of the solvent. Lovastatin was crystallized by the addition of water to give an acetonitrile concentration of approximately 25-30%. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered in an overall yield of 91%.

EXAMPLE 4

4.6 g of crude lovastatin was dissolved in 200 mL of 70:30 acetonitrile/water buffered with 0.02 M Tris-acetate (pH 7.5). The solution was loaded onto a 5 cm diameter, 25 cm long column packed with 10 μm, irregular-shaped octadecylsilane HPLC packing (RG1010-C18, The PQ Corpodration, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The lovastatin fraction was collected in a volume of 265 mL using UV detection at 254 nm. The lovastatin peak eluted at K' = 2.0-3.0. The resulting solution was concentrated

by removal of two-thirds of the solvent, which crystallized the lovastatin. The pure lovastatin product was recovered by filtration and drying. Lovastatin with a purity of 99.7% w/w was recovered in an overall yield of 91%.

EXAMPLE 5

Lovastatin at a concentration of 4.5 g/100 mL was dissolved in a mixture of 70% acetonitrile/30% 0.02 M Tris-acetate (pH 7.2). The 40°C solution was injected onto a 5 cm diameter, 25 cm long stainless steel column packed with 10-20 μm, irregular-shaped octadecylsilane HPLC packing (RG1020-C18, The PQ Corporation, Conshohocken, PA). The eluant was 70:30 acetonitrile/water and the flow rate was approximately 150 mL/min. The media and column were isothermally maintained at 40°C. The lovastatin fraction was collected in a volume of 500 mL using UV detection at 254 nm. The lovastatin fraction eluted at $K' = 2.0-3.0$. The resulting solution was concentrated by removal of two-thirds of the solvent and the lovastatin crystallized. The lovastatin was recovered by filtration and drying. Lovastatin with a purity 99.8% w/w was recovered in an overall yield of 90%.

EXAMPLE 6

6.0 g of the purified lovastatin prepared as described in Example 5 was dissolved in 100 mL of 95% methanol/5% water at 60° C. The 60° C solution was crystallized by the addition of an equal volume of 65% water/35% methanol. The resulting crystalline mixture was concentrated to one half volume. Lovastatin was recovered by filtration and drying. 5.98 g of lovastatin was recovered.

EXAMPLE 7

Simvastatin may be purified to a crystalline form of purity greater than 99.5% using procedures analogous to those described in Example 5. Crude simvastatin is used in place of crude lovastatin.

EXAMPLE 8

Pravastatin may be purified to a crystalline form of purity greater than 99.5% using a procedure analogous to that in Example 5, but substituting crude pravastatin for the crude lovastatin.

WHAT IS CLAIMED IS:

1. A process for purifying a crude HMG-CoA reductase inhibitor which comprises:

(1) placing a solution of the crude HMG-CoA reductase inhibitor on a high performance liquid chromatography column wherein said column is packed with silica optionally coated with a stationary phase selected from a group consisting of a triorganosilyl, a cyanoorganosilyl or a polystyrene-divinylbenzene copolymer with an organosilyl, or said column is packed with a porous graphitic carbon;

(2) eluting with a solvent mixture comprising:

(a) an organic solvent selected from a group consisting of acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride or chloroform, or a mixture thereof and optionally

(b) water or an aqueous solution selected from: phosphoric acid, acetic acid;

(3) removing about 30 to 35 percent of the solvent mixture from the eluted fraction containing HMG-CoA reductase; and

(4) treating the eluted fraction containing HMG-CoA reductase inhibitor fraction with water to crystallize the HMG-CoA reductase inhibitor.

2. A process of Claim 1 wherein the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin, pravastatin, fluvastatin or mevastatin.

3. A process of Claim 2 wherein the HMG-CoA reductase inhibitor is selected from lovastatin or simvastatin.

4. A process of Claim 2 wherein the HMG-CoA reductase inhibitor is lovastatin.

5. A process of Claim 3 wherein the column is packed with a silica coated with an octadecylsilane stationary phase.

6. A process of Claim 5 wherein the solvent mixture is acetonitrile and water.

7. A process of Claim 6 wherein the solvent mixture is 70% acetonitrile and 30% water.

8. A process of Claim 7 wherein the operating temperature of the chromastography is between 15° to 60°C.

9. A process of Claim 8 wherein about one-third of the solvent mixture is removed from the eluted fraction containing the HMG-CoA reductase inhibitor.

10. A process of Claim 1 further comprising the filtering and drying of the HMG-CoA reductase inhibitor to yield a product of purity $\geq$ 99.5%.

11. A process for purifying a crude HMG-CoA reductase inhibitor which comprises:

(1) placing a solution of the crude HMG-CoA reductase inhibitor on a high performance liquid chromatography column wherein said column is packed with silica optionally coated with a stationary phase selected from a group consisting of a triorganosilyl, a cyanoorganosilyl or a polystyrene-polystyrene-divinylbenzene copolymer with an organosilyl, or said column is packed with a porous graphitic carbon;

(2) eluting with a solvent mixture comprising:

(a) an organic solvent selected from a group consisting of acetonitrile, methanol, ethanol, acetone, tetrahydrofuran, isopropanol, ethyl acetate, methylene chloride or chloroform, or a mixture thereof and optionally

(b) water or an aqueous solution selected from: phosphoric acid, acetic acid; and

(3) removing about 60 to 65% of the solvent mixture from the eluted fraction containing HMG-CoA reductase inhibitor to crystallize the HMG-CoA reductase inhibitor.

12. An HMG-CoA reductase inhibitor of purity at least 99.5% or a pharmaceutically acceptable salt thereof.

13. A compound of Claim 12 wherein the HMG-CoA reductase inhibitor is selected from the group consisting of lovastatin, simvastatin and pravastatin or a pharmaceutically acceptable salt thereof.

14. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is lovastatin.

15. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is simvastatin.

16. A compound of Claim 13 wherein the HMG-CoA reductase inhibitor is pravastatin.

17. An HMG-CoA reductase inhibitor purified by a process comprising high performance liquid chromatography and wherein the HMG-CoA reductase inhibitor has a purity of at least 99.5%.

18. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 12 and a pharmaceutically acceptable carrier.

19. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 12 in combination with a pharmaceutically acceptable nontoxic cationic polymer capable of binding bile acids in a non-reabsorbable form in the gastrointestinal tract and pharmaceutically acceptable carrier.

20. A pharmaceutical composition comprising a nontoxic therapeutically effective amount of a compound of Claim 12 in combination with a nontoxic therapeutically effective amount of a cholesterol lowering agent selected from the group consisting of:

(a) Squalene synthetase inhibitor;
(b) HMG-CoA synthetase inhibitor;
(c) Squalene expoxidase inhibitor;
(d) Probucol;
(e) Niacin;
(f) Gemfibrozil; and
(g) Clofibrate.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US92/01364

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): B01D 15/08
US Cl.: 210/656; 435/125

II. FIELDS SEARCHED

Minimum Documentation Searched

Classification System	Classification Symbols
U.S.	210/198.2, 635, 656; 422/70; 435/125; 436/161; 514/356, 451; 514/460, 543, 571, 642, 643, 712, 824; 549/292

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched

III. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	US, A, 4,533,494 (UCHIYAMA) 06 August 1985 See the entire document	1-11
X Y	US, A, 4,997,755 (WILLIAMSON) 05 March 1991 See the entire document	2-8,12-14,17 1,9-11,15-16
Y	US, A, 4,833,258 (SMITH) 23 May 1989 See the entire document	1-11
Y	US, A, 4,965,200 (CHEN) 23 October 1990 See the entire document	1-11
Y	US, A, 4,719,229 (REAMER) 12 January 1988 See the entire document	1-11
X	US, A, 4,231,938 (MONAGAN) 04 November 1980 See the entire document	12-14
X,P	US, A, 5,089,523 (VARMA) 18 February 1992 See the entire document	1,18-20
X,E	US, A, 5,099,035 (SAUNDERS) 24 March 1992 See the entire document	12,18-20

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
28 April 1992	15 JUN 1992
International Searching Authority	**Signature of Authorized Officer**
ISA/US	for Sun Uk Kim NGUYEN NGOC-YEN INTERNATIONAL DIVISION

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FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

X,E	US, A, 5,102,911 (LEE) 07 April 1992 See the entire document	12,18-20
X	The Merck Index, 11th Edition, Published 1989 (Rahway, New Jersey) See compounds 5460, 7712, 8491	12-16

V ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE[1]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1 ☐ Claim numbers because they relate to subject matter[2] not required to be searched by this Authority, namely:

2 ☐ Claim numbers , because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out[3], specifically:

3 ☐ Claim numbers , because they are dependent claims not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING[3]

This International Searching Authority found multiple inventions in this international application as follows:

1 ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2 ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3 ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4 ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☐ No protest accompanied the payment of additional search fees.